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DEVELOPMENT OF ANTIBODIES FOR BACILLUS TYPHI-EXANTHEMATICI IN TYPHUS FEVER CONTACTS *

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In a previous publication,¹ 2 observations were reported which indicated that individuals who are exposed to typhus fever may react with the production of specific antibodies without having had any clinical evidences of the disease. During the past year, the number of such observations have multiplied, so that it now seems as if the phenomenon were by no means uncommon. These observations are unquestionably of considerable etiologic as well as epidemiologic significance; it has, therefore, been thought advisable to report them now in detail.

The first observations were made in New York, and for the serologic work in these cases I am indebted to Dr. Peter K. Olitsky; the later ones were made while studying a recent typhus epidemic in Volhynia, Russia. Complement fixation tests were made with a typhus antigen, consisting of the clear Berkefeld filtrate of a 24-hour autolysate of *Bacillus typhi-exanthematici*, previously killed by heating to 60 C. for an hour (for detailed technic, see paper by Olitsky¹). This antigen is absolutely specific, giving positive reactions only with the serum of typhus convalescents and in the group of cases reported in this paper. Uniformly negative results have been obtained in 150 control cases, including a great variety of acute and chronic febrile diseases and other pathologic conditions.

The agglutination tests were carried out with a polyvalent agglutinogen whenever possible, and the microscopic method was used for reasons detailed in a previous paper.¹ Agglutinins, as a rule, first appear in the blood during the second week of typhus fever, and increase rapidly at the crisis. On the average, the maximum titer is attained during the second week of convalescence; the agglutinins then

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¹ Plotz, Olitsky, and Baehr, *Jour. Infect. Dis.*, 1915, 17, p. 1.

gradually diminish, but disappear from the blood, as a rule, only after many months. As I was recently able to show,² the curve of the specific agglutinins in typhus fever is characteristically an immunity curve, rising with recovery and the development of immunity, persisting for a long time, then gradually and slowly diminishing.

On nontyphus cases, Dr. Olitsky, Dr. Plotz, and I have now done over 200 agglutination tests. Occasionally, nonspecific agglutination has been observed in low dilutions of serum, a phenomenon common to most bacteria. Only twice have we seen an agglutination with serum of a nontyphus case in a dilution as high as 1:50. In higher dilutions, agglutination has only been observed in individuals who have or have had typhus fever, or who have been vaccinated with *Bacillus typhi-exanthematici*, and in the group of cases which forms the subject of this report. This last group includes all those patients in whom we have found a high antibody content and who clinically have not had typhus fever.

In view of the otherwise negative serologic findings in nontyphus cases, these observations are interesting and important. The first two cases were reported in a previous paper.¹

CASE 1.—Toward the end of 1914, after carrying on experimental and other work on typhus fever for over six months, Dr. B. experienced some slight malaise and general muscular pains for a few days, but they were not marked enough to require any attention. Three or 4 weeks later, his blood was examined serologically, preliminary to the proposed administration of vaccine. Much to our surprise, the serum gave a ++++ complement-fixation with typhus antigen and agglutinated typhus bacilli in a dilution of 1:500. As we had observed serologic reactions of this degree only in individuals who were convalescing from typhus fever, we had reason to suspect that Dr. B. had recently passed through an infection, although he had shown only slight clinical manifestations of illness. This was in a manner confirmed by the fact that, as in convalescents from typhus fever, the serologic phenomena gradually diminished in intensity after the first month, so that by the end of 4 months, both complement-fixation and agglutination became practically negative.

TABLE 1
RESULTS OF SEROLOGIC TESTS

Time of Test	Complement-Fixation	Agglutination
Dec. 15, 1914	++++	1:500 +
Dec. 21, 1914	++++	1:200 +
Mar. 1, 1915	++	1:50 +
Apr. 17, 1915	negative	1:20 +

Previous to these observations, Dr. B. had been in contact with patients suffering from the mild New York typhus, but usually only after their clothing had been removed and they had been bathed. Dr. B. also bled typhus guinea-

² Jour. Infect. Dis., 1917, 21, p. 21.

pigs and monkeys almost daily for the purposes of study, virus transmission, etc. No special precautions were taken to avoid infection, the virulent blood of infected animals often remaining on his hands throughout a series of experiment lasting over an hour. That an infection can be produced in human beings by direct inoculation of typhus blood has been amply demonstrated by Moczutkowski,³ Otero,⁴ Yersin and Vassal⁵ and others. So it is possible that Dr. B.'s infection could have occurred without the usual intermediary agency of the body louse.

CASE 2.—With this observation in mind, similar examinations were made on two nurses, Miss L. and Miss H., who had just returned from Serbia where they had been nursing typhus fever patients during the big epidemic of 1914-1915. Many of the patients under their care had been covered with vermin. Miss L. believed that she had been repeatedly bitten by lice and that on at least two occasions she had removed lice from her clothing. The serologic studies on Miss H. were negative. The serum of Miss L. gave a +++ fixation with typhus antigen and firmly agglutinated typhus bacilli in a dilution of 1:200.

CASES 3 AND 4.—A Macedonian immigrant left the town of Florina, near Monastir, in Macedonia, on March 1, 1915, arriving in Salonica on the same day. On March 2, he left Salonica on a packet boat for Piraeus, and on March 3, sailed from Piraeus on a Greek steamer for New York. The steamer touched at Kalamata, Patras and Algiers, enroute, and arrived in New York, March 23. He immediately left New York by rail for East Syracuse, arriving there March 24. He experienced the first symptoms of illness, April 7 and was acutely ill, April 9, the disease ending with the defervescence of temperature, April 19, the twelfth day of illness. The case was definitely diagnosed as typhus fever by Dr. John L. Kantor⁶ who had had experience with the disease in New York. On the tenth day of illness, complement-fixation was negative, but his serum agglutinated typhus bacilli in a dilution of 1:100. Five days after the crisis his complement-fixation was still negative, but his serum agglutinated in a dilution of 1:1800. No further examinations were made.

The mode of infection in this case was definitely ascertainable. During the two weeks following February 21, there were six deaths from typhus fever in Salonica. According to the patient's story he was free of vermin until he boarded the packet boat at Salonica. Both the packet boat and the steamer on which he subsequently traveled to New York were in a filthy condition, and by the time the vessel arrived in New York, most of the steerage passengers harbored body lice. As his illness began on April 7, the infection must have occurred on shipboard.

Four other Macedonians roomed with him in Syracuse, one of whom had been with him on his sea journey. None of them subsequently developed the disease. The blood of all 4 was examined serologically on April 27. In 2 of them, complement-fixation and agglutination were negative. The other 2, however, had a ++ complement-fixation and their serum agglutinated the typhus bacilli in dilutions of 1:200 and 1:300, respectively.

³ St. Petersburg. med. Wchnschr., 1900, 25, p. 30. Allg. med. Centr.-Ztg., 1900, 69, p. 1055.

⁴ Memoria presentata a la Acad. de Medicina de Mex., Mexico City, 1907.

⁵ Philippine Jour. Sc., 1908, 3, p. 131.

⁶ Jour. Infect. Dis., 1915, 17, p. 522.

CASE 5.—W. P. had charge of the animals used by us at the Mount Sinai Hospital in New York and also assisted us with all our experimental work. The mode of infection in his case is as obscure as was that of Dr. B., and might also have occurred without the agency of the louse. It is of interest to note that he handled dozens of typhus-infected monkeys and guinea-pigs daily, and also frequently came in contact with virulent typhus blood.

TABLE 2
RESULTS OF SEROLOGIC TESTS

Time of Test	Agglutination	Complement-Fixation
April 27, 1915.....	1:500	++++
Sept. 10, 1915.....	1:200	++++

CASE 6.—Dr. U. has practiced medicine in Mexico for many years. During the past year, there has been a large epidemic of typhus fever in Mexico City and Dr. U. treated many cases. About six months ago, his wife and his daughter contracted the disease, but Dr. U. remained absolutely well. Recently while on a visit to New York, we had an opportunity to examine Dr. U.'s blood. It showed a complement-fixation of +++ and an agglutination of 1:200.

The conditions in Russia were especially favorable for the investigation of this problem because of the careful precautions taken by the Austro-Hungarian military authorities for the quarantining of typhus fever patients and those who had been in contact with them. Volhynia and Russian Poland were studded with typhus hospitals and hospitals for epidemic diseases. On the outbreak of typhus fever in a community, the individuals who had been in contact with the patients were immediately confined in the quarantine building of the typhus hospital. Here they were in the charge of a nurse; they were visited twice daily by a physician, and their temperatures were recorded 3 times a day. On the appearance of the first prodromal symptoms of illness or the slightest rise in temperature above the normal, the suspect was immediately transferred to the observation ward of the hospital.

CASE 7.—On January 9, a family of six people, father, mother and 4 daughters, were sent to the typhus hospital from a village where typhus fever had recently become epidemic. On admission, 3 daughters were in the second week of a typical typhus fever of moderate severity and the mother was in the third day of the illness. The mother's illness lasted 15 days, but was for the most part so mild that if the patient had not been confined to the hospital, hers would undoubtedly have been an ambulatory case. All 4 patients developed agglutinins in their blood toward the end of their illness.

On the ninth day of the illness, the mother's serum agglutinated the typhus bacillus in a dilution of 1:200; on the fourteenth day, 1:200. During convalescence, agglutinins were found in the blood in a dilution of 1:500, on the third day; 1:300, on the seventh day, and 1:300, on the eleventh day. Agglutinins were found in the blood of the first daughter on the sixteenth day of the illness in a dilution of 1:100; on the third day of convalescence, 1:100; on the seventh day of convalescence, 1:50. The blood of the second daughter was not examined during illness; on the second day of convalescence, the

serum agglutinated the typhus bacillus in a dilution of 1:500; on the seventh day, 1:200. In the blood of the third daughter, agglutinins were found on the fourteenth day of the illness in a dilution of 1:50; during convalescence, it was not examined.

On admission to the hospital, only the father and the youngest daughter were free from the disease. The girl remained well and her temperature was normal until the tenth day after her admission. On that day she complained of headache and chilly sensation and the temperature rose to 37.8 C. On the following day, she had a severe chill and the temperature rose to 40.2 C. The rash first appeared on the evening of the fourth day and from then on her disease ran a typical course of moderate severity, ending by crisis on the fifteenth day. The typical clinical picture was confirmed by the bacteriologic and serologic findings. Three blood cultures, taken on the first, fifth, and eleventh days of the disease, were all positive; in the first culture, taken at the time of the initial chill, 168 colonies developed in 12 c.c. of blood. Agglutination of *Bacillus typhi-exanthematici* by the patient's serum was negative before the onset of the illness; positive 1:50, on the eighth and twelfth days, and positive 1:100, on the first and fifth days of convalescence.

The only member of the family who failed to develop the disease was the father. He remained well and the temperature never rose above normal during the entire 4 weeks after exposure, during which he was in quarantine. At this time, the blood was examined 3 times for agglutinins. On the second day of admission, the results were negative; on the seventh day, agglutinins were found in a dilution of 1:50; on the twentieth day, 1:100. So, of the 2 members of the family who were still well at the time of admission, one subsequently developed the disease, whereas the other, who remained well, simultaneously developed in his blood specific agglutinins for *Bacillus typhi-exanthematici*.

CASE 8.—Two Austro-Hungarian nurses belonging to the staff of a mobile epidemic hospital situated on the Russian-Galician frontier were assigned to temporary duty in a distant Russian village where typhus fever was epidemic. They lived in a small hut with a peasant family, all the members of which were severely ill with typhus fever. One did the nursing during the day, the other was on duty at night. The patients were infested with lice, and the nurses were unable to protect themselves from the vermin. Under these primitive conditions they lived for three weeks, when they were relieved and reassigned to hospital duty. Six days later one of the nurses developed typhus fever. We saw her on the eighth day of her illness, at which time she had an extensive and typical rash and presented the characteristic picture of the disease. A blood culture taken on this day was positive, 3 colonies of *Bacillus typhi-exanthematici* developing in 10 c.c. of blood. Her serum also agglutinated the typhus bacillus in a dilution of 1:100.

The second nurse had similarly been exposed to typhus fever for 3 weeks, but had subsequently remained well, nor had she previously ever been ill. Her blood was examined on the same day as that of the sick nurse, two weeks after being relieved from her previous typhus duty. It agglutinated the *Bacillus typhi-exanthematici* up to a dilution of 1:500.

CASES 9 TO 12.—A family of eleven individuals lived together in a typical, squalid peasant hut, situated in the Russian village of Rahozno, where typhus fever had recently become epidemic. In the early part of December, 1915, the mother and 4 of the children became severely ill with typhus fever. The entire family was then immediately transferred to the typhus hospital, the sick

individuals to the wards, and those who had remained well to the quarantine building. The 5 sick members of the family presented the typical picture of the disease, the mother dying December 19. The autopsy revealed the usual more or less negative findings of typhus fever. The remaining six members of the family were under constant medical observation both during the 4 weeks' sojourn at the hospital, and subsequently at their home, and at no time did they have the slightest rise in temperature. Four weeks after the death of the mother, we were able to procure some blood from 5 of the 6 members; their serum agglutinated *Bacillus typhi-exanthematici* in the following dilutions:

Wasył	1: 50 +
Alexandra	1: 200 +
Hanna	Negative
Wartha	1: 100 +
Maria	1: 200 +

CASE 13.—The Jasinoſky family, neighbors of the Choročovskys, consisted of seven individuals, and they had lived in one room since the end of September, 1915. Five of the 7 were subsequently ill with typhus fever, 4, during the month of October and the fifth, during November. The existence of typhus fever in this house was not discovered by the military authorities until the beginning of November, when the fifth member of the family became ill. The entire family was then brought to the hospital, "entlausst," and kept under observation. Here, the man who was still ill, ran the typical course of typhus fever, ending in recovery on November 15th. Two months later, we had the opportunity of examining the blood of 5 members of this family. Of these, 2 had had the disease in October and one in November. Agglutination of *Bacillus typhi-exanthematici* was obtained with their serum in the following dilutions:

Maxim	1: 100 +
Wasył	1: 150 +
Andreas	1: 50 +

The results of similar examinations made upon the 2 members of the family who had escaped the illness were as follows:

Priska	1: 300 +
Stefan	Negative

CASES 14 AND 15.—The head of another family, T., had typhus fever from November 10 to 25. In the second week of his illness, he and the members of his household, his wife, sister-in-law and mother-in-law, were transported to the typhus hospital, where they were under observation for 4 weeks. Previous to that time, the family had lived in a 2-room house, T. and his wife in 1 room and the sister-in-law and mother-in-law in the other. The former room also served as a living- and dining-room for the family. During their stay at the hospital, none of the family, with the exception of T., showed the slightest rise of temperature, nor did they suffer from any illness either before or after this time. Two months after T.'s illness, blood was secured from these 3 members of the family and examined for agglutinins, with the following results:

Wife	1: 50 +
Mother-in-law	Negative
Sister-in-law	1: 100 +

CASE 16.—At the typhus hospital in Volhynia, in which most of these observations were made, only people who had once had typhus fever were employed as doctors, nurses and orderlies. But in addition to this staff, there were 11

nonimmunes, men who had not had the disease, employed about the hospital as mechanics, carpenters and general workmen. These men had their living quarters apart from the rest of the staff, but it was not always possible to keep them from coming in contact with men on duty in the wards or in the reception room of the hospital, or with those whose duty it was to transport typhus patients in ox-carts from the village to the hospital. In view of their residence in a typhus hospital, the possibility of infection could not, therefore, be avoided, and for this reason the blood of these 11 men was examined for agglutinins. All were negative with one exception; a carpenter who had been working at the hospital for 4 months, but had been well during that entire time. His serum strongly agglutinated *Bacillus typhi-exanthematici* to a dilution of 1:200.

CASE 17.—Another man, M., denied having been ill. On admission to the quarantine hospital, his temperature was 38 C., but was normal thereafter. Upon examination, his skin showed what the clinicians at the hospital thought was suspiciously like a recently faded typhus rash. The patient also looked ill and worn, as if he had recently been through an illness. Upon questioning his wife, she also denied that he had been ill, but said that for the last 10 days he had acted stupidly, though he had otherwise gone about as usual. From the general appearance of the patient, the suspicion was very strong that he had just been through a mild ambulatory typhus, and the authorities, therefore, sent him to the typhus hospital. Their suspicion was then still further confirmed by the agglutination tests which were made without any knowledge of the foregoing facts. Tests made on 2 occasions showed a strong agglutination in a dilution of 1:100. It was later learned, through subsequent investigation, that his sister-in-law's husband had had typhus fever about 4 weeks previous. But when an attempt was made by the military authorities to quarantine the family, this sister-in-law had escaped and had gone to live with the M.'s family.

CASES 18 TO 20.—The attendants working in the reception room of a hospital where typhus fever patients are daily being admitted are especially liable to infection. Their duty is to "cleanse" the patient, remove his vermin infected clothing and bathe and shave him. As a rule men who have had typhus fever are assigned to this duty. But often, especially at the onset of an epidemic, the demand for such people has been greater than the supply, and nonimmunes were then employed. Many of these men succumbed to infection. But we have found 3 such individuals who, in spite of the constant exposure to infection, have never had any symptoms of illness, and in their blood we have found agglutinins for the *Bacillus typhi-exanthematici*. In 2, agglutinins were found in a dilution of 1:100; in the third, in a dilution of 1:200.

SUMMARY

These 20 observations include all the cases observed by us, which did not have typhus fever clinically, but in whose blood specific antibodies in high titer were found. Every one of these 20 individuals was found to have recently been in intimate contact with typhus fever. They were either doctors, nurses and hospital attendants who were handling typhus fever patients, or they were friends or members of families in which typhus fever had recently occurred. The latter had

lived in the same room with their sick relatives or friends, or had been in close association with them. The significance of these observations can be really appreciated when we realize that in over 250 other non-typhus controls, who, with few exceptions, had not been in contact with typhus fever patients, complement-fixation was never observed and specific agglutinins were not demonstrable in a dilution above 1:50.

Of these 20 typhus contacts, 3, after their exposure to infection, had had vague, general symptoms indistinguishable from an influenza. All the others had been well. Shortly after their exposure, the sera of these contacts were found to contain specific antibodies in amounts otherwise only observed by us in individuals who have recently recovered from typhus fever. These findings permit of only 1 interpretation, that at the time of their exposure, the contacts had actually been infected with the bacilli, but in quantities insufficient to induce the clinical manifestations of the disease. The phenomenon is comparable to what one would expect from the inoculation of a subinfective dose of the virus or of virulent bacilli, especially if such an inoculation were frequently repeated.

Whether such contacts after they have developed a high antibody titer in their blood are permanently immune to the disease, cannot, of course, be ascertained with any positiveness. We are only in a position to say that most of these people continued to live in the midst of a typhus epidemic for some months and none of them developed the disease. In this regard, however, some of the experimental work which has been done on monkeys is undoubtedly of some significance. Nicolle, Conor and Conseil,⁷ Ricketts and Wilder,⁸ and Anderson and Goldberger⁹ have independently noted that monkeys which have been exposed to the bites of infected typhus lice may subsequently develop an immunity without having had fever or any other sign of illness. It is therefore quite reasonable to suppose that the same thing may occur in human beings after a similar exposure to infection, especially in view of the additional serologic evidence which we have accumulated.

We have now met with 20 such instances during the course of our work, without having made any systematic search. Such individuals who have become immune without actually having had the disease cannot therefore be very uncommon. And they are a serious danger epidemiologically, for they may act as carriers of the infected lice and

⁷ *Compt. rend. Acad. d. sc.*, 1909, 149, p. 149.

⁸ *Jour. Am. Med. Assn.*, 1910, 54, p. 1304.

⁹ *Collected Studies on Typhus Fever*, Bull. 86, Hyg. Lab., U. S. P. H. S., 1912.

be the agents of their distribution throughout a community. This is no theoretical consideration, for da Rocha Lima has recently demonstrated experimentally that typhus lice when kept alive by repeated feedings on typhus immune individuals do not lose their virulence for a long time.

The general immunologic principle deducible from the observations which are here reported are probably generally applicable to other infectious diseases besides typhus fever. That mild abortive forms of the various infectious diseases are followed by an immunity is generally recognized. The suspicion has also been voiced that people may become immune following a simple exposure to some of the infectious diseases, even though at the time they have shown no signs of illness. Up to the present, however, there has been no direct scientific evidence that this does occur.

The observations recorded in this paper are of importance from another aspect. The observation that individuals after exposure to typhus fever may fail to develop the disease, and yet may react with the production of specific antibodies against *Bacillus typhi-exanthematici* is incontrovertible evidence as to the etiologic significance of this organism. The phenomenon cannot possibly be explained on any other ground than that the *Bacillus typhi-exanthematici* is the cause of typhus fever.